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AIDS - its nature and origin

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Pathology

The outbreak of full-blown AIDS corresponds to a dramatic break-down of the immune function of the patient. It is the end phase of a pathogene process in the T4-lymphocytes, caused by a virus and mostly drown out over years.

T4-lymphocytes play an essential role in the immunisation process. We know that the antibodies, the actual vehicles of the immune function, are produced by B-lymphocytes (bone marrow), so called because their stem cells are formed in the red bone marrow. In that process the B-lymphocytes transform into plasmocytes, which bear the information required for the formation of the antibody in the genome of the cell. They can then synthetise the antibody, a protein of the globulin group, but at the same time they also become "memory cells", which retain the ability to form a certain antibody over a long space of time, frequently for the duration of life.

This transformation into plasmocytes is steered by T-lymphocytes, so called, because their stem cells derive from the thymus gland. There are twi groups of them: One of these groups regulates and supports the formation of B-plasmocytes; they are known as helper cells. The other group bears membrane bound antibodies, that link up with invading alien cells, destroy them and hence derive the name of killer or suppressor cells. Helper and killer cells are distinguished by different kinds of receptors on their cell surface. Helper cells have OKT-4 receptor. Killer cells the OKT-8 receptor; this has led to the usage of referring to them as T4-cells and T8-cells respectively.

The linkage of a virus particle to a cell and its later penetration into it requires the presence on the virus' envelope of a molecule which fits to one of the surface receptors of the cell; it is called a "marker". Unfortunately one of the envelope proteins of the AIDS virus has a marker for the OKT-4 receptor. If an AIDS virus particle enters the blood stream, it links up preferently with a T4-cell, penetrate it, and its genome will

In contrast to many other types of viruses, the AIDS virus does not kill the infect cell. New virions will be formed inside the cell, they pass to the cell membrane and are expressed by budding, with no apparent significant damage to the cell. Nos is its helper-function impaired to begin with, and the immune activity remains normal. The virus genome, however, installs a trans-activator into the cell, which intensifies its metabolism by roughly 1000 times, enforcing its proliferation. Lymph nodes, "lymphadenomae" are formed, which are not tumours by nature, and which are spontaneously reduced in the course of time. This process is described as lymphadenopathy, and, together with a number of other light symptoms, as Lymphadenopathy Associated Syndrome (LAS), or Prae-AIDS, or AIDS-Prodrome.

That definition is mostly unjustified. In approximately 90 per cent of these cases AIDS will not be developed. In the patient's serum antibodies against the virus will mostly be found, and virus cultures may be bred from the serum or the cells but after about 2 years the symptoms will recede and recovery will begin.

In about 10 per cent of all cases there will be a marked reduction of T4-cells. Whereas the proportion of the number of T4/T8-cells was normally approximately 2/1, it is reduced to 0.5/1 or less, and the remaining T4-cells completely lose their helper function. In this way the AIDS virus has played its part. Full-blown AIDS develops on the basis of a complete loss of the immune function due to the degeneration of the T4-cells; the virus has no further part in the process.

Opportunistic disease

It would appear that an organism without immune protection allowed all kinds of diseases to develop freely. Yet this is by no means the case. In as far as memory cells with the information for the formation of a given antibody are produced prior to AIDS infection, the patient can bring forth that antibody even after destruction of the helper-cells. He will not, therefore, contract measles or chickenpox a second time. The opportunist

way in which they were caught. Closer investigation will supply the explanation.

Let us consider, as a first example, cytomegalia, a disease in which abnormally large cells are formed, obstructing normal organic functions. The symptoms of this disease are particularly marked in the salivary glands, but the most serious damage occurs in the internal organs, particularly in the liver. Its pathogene is the cytomegalovirus (CMV), belonging to the herpes virus family.

In Europe between 40 and 100 per cent of all adults are CMV carriers, varying from country to country. Contamination usually begins after the first year of life. There are no symptoms of disease linked with it, since the immune defence pushes back the virus to the interior of the cells, where it forms a repressed gene complex. The infection only becomes dangerous in case it is contracted by infants with not yet developed immune function. In such cases dangerous diseases occur. The same happens, of course, in cases where AIDS interrupts the immune function; then cytomegalia assumes a lethal character.

Even before the first appearance of AIDS, an increased frequency of cytomegalia could be noted. Those affected were patients receiving immunosuppressive treatment, either for autoimmune diseases with serious symptoms - rheumatism, lupus erythematodes - or in connection with organ transplantation. The CMV is not concerned by the causes of immune deficiency. The same applies in regard to numerous other pathogenes normally suppressed by immune defences. Opportunistic infections are caused by fungous diseases, protozoa, bacteria or viruses. These diseases are rare, because most people have adequate immune defences, but their pathogenes are ubiquitous and they take advantage of all opportunities to become effective.

The emergence of a serious disease on the failure of the immune system does not of necessity require a pathogenic micro organism. Let us take Kaposi's Sarcoma (KS), a skin cancer with numerous foci, at first described in the last century as an old men's disease, apparently with a close geographical range. In

Europe KS was noted in the Danube delta, the Po plain, in Sardinia, in the coastal regions of Greece - i.e. in typical malaria regions. Lately several authors (Whittle et al.[1]; Epstein[2]; Bigger[3]; etc.) have pointed out that malaria caused an immuno-depression which may become active in combination with other immunodepressive factors, as a co-factor.

We know that immune activity decreases in advantage age, particularly among men, and thus age-conditioned KS occurs in malaria regions in combination with immunodepression.

We are fairly well informed today about the mechanism of the KS formation. In every cell division there are very slight prospects of the cell transformation into a tumour cell. In highly proliferating tissue, also including our skin, the cells of which are constantly renewed from the interior, numerous microtumours will be formed sooner or later, which, however, do not constitute any serious danger. The work of Burnet[4] revealed, that these tumour cells, with their changed metabolism are singled out by the immune mechanism as "not pertaining to the body" and destroyed. That immune barrier is broken down only in rare exceptions so that cancer remains an exceptional case. If, however, the immune mechanism is weakened by age and malaria, or, in recent times, by immunosuppressive treatment, many of these microtumours survive and the pathological symptoms of KS emerge.

If the immune system is completely excluded by AIDS, the process inevitably becomes particularly dramatic. In this case the tumours do not react to chemotherapy, they disseminate intensely and soon lead to the patient's death. Approximately 25 per cent of the AIDS patients die of Kaposi sarcoma.

We have seen that in the case of immunosuppression the cytomegalovirus, so far repressed, is fully developed. This is how in many KS patients free CMV virions were noted, which in the first place led to the assumption that KS was caused by the CMV. In the meantime so numerous cases of KS without CMV have been described, that today the opinion prevails that KS spontaneously arise in the presence of immune deficiency, requiring no further pathogene. It is concluded, that this is

AIDS and the central nervous system

In approximately one third of all AIDS cases diseases of the central nervous system are observed, which were at first interpreted as opportunistic infections. Unfortunately we dispose increasingly over observations which testify to direct damage of the CNS caused by the AIDS virus. Thus, in several cases damage to the brain cells was established before the significant reduction of the patient's immune activity (Black[5]). Specific antibodies against the virus were identified in the liquor, with a higher titer than in the blood, which excludes the infiltration of antibodies from the blood (Resnik et al.[6]). In numerous cases virus was identified in the cerebrospinal liquor or in the damage cells under the electronic microscope (Ho et al.[7]). In recent times there has been unanimity in the assumption that the AIDS virus is both lymphotropic and neurotropic, i.e. that it may be a parasite on lymphatic cells (in particular T4-cells) as well as on neurons. We have seen that the virus has a marker on its envelope, by means of which it fastens to the OKT-4 receptor of the T4-cell. The virus must therefore also have another marker which fits to a receptor of t. membranes of nerve cells as yet unidentified, allowing fastening and infection there.

In the following chapter we shall see that a large part of the genome of the AIDS virus is almost identical with part of the genome of the Visna virus, a pathogene which causes serious brain diseases in sheep. It may be assumed that in this common part of the genome the gene for the envelope protein is also present, acting as a marker for the receptor of the neuron cell membrane.

Both, the Visna infection and AIDS are characterised by the very gradual development of the disease. Visna is considered to have incubation periods between 1 and 14 years. This Visna virus is a typical representative of the lentivirus (slow virus) group. Most research specialists also include the AIDS virus in this subcategory of retroviruses.

The virus

As early as in the summer of 1983 a French research group at the Pasteur Institute in Paris, headed by Luc Montagnier, succeded in isolating the virus from a French AIDS patient who had become infected in New York; they also managed to breed a pure culture of the virus. It was given the non-committal name of "Lymphadenopathy Associated Virus" (LAV)[8]. Approximately three month later the same was achieved by an American research team headed by R.Gallo[9]. Their virus was also identified in a patient from the American East coast. It got the name HTLV-III which will be discussed later on. Some time after this, an American research team headed by P.A.Luciv identified a virus in a patient from the West coast, which was named "AIDS Related Virus" (ARV)[10]. Subsequent investigations of the genom of the three viruses revealed that LAV and HTLV-III were almost identical and that the ARV was only slightly different, so slightly, that the deviations could easily be explained by mutations. Today there is unanimity about the fact, that it is the same virus, and that it is certainly the virus causing AIDS. It may be reproduced in cell cultures of T4-lymphocytes, it is therefore T4-lymphotropic, it binds the antibodies found in the blood or liquor of AIDS patients, and it can be isolated from the blood or tissue of AIDS or prae-AIDS patients.

Even before AIDS became a problem, Gallo [11] had discovered another T4-lymphotropic virus, the pathogen of a T4-lymphoma, resulting from the uninhibited and unlimited division of T4-cells. He named it "Human T-cell Leukemia/Lymphoma Virus" (HTLV). Subsequently he discovered a slightly deviating form, the pathogen of the hair cell lymphoma. He consistently named the originally discovered form HTLV-I and the new one HTLV-II. When he isolated a new virus from AIDS patients, also T4-lymphotropic, he assumed to begin with that this was a close relation of the HTLV viruses known hitherto, and named it HTLV-III. He was not entirely unjustified in this, since there were clear immunological cross-reactions between them; they at least had a few proteins similar in structure and therefore had to contain correspondingly similar genes in their genom.

This led Gallo to a first hypothesis on the development of AIDS, which he did not publish in professional journals, but elucidated in mass media on several occasions[12]. He departed from the fact, that the HTLV-I was endemic in a region extending from Japan to South East Asia, Central Africa, the Caribbean as far as the southern states of the USA. At some point the HTLV-I was said to have changed into the similar form of the HTLV-III. AIDS had therefore developed as a result of a regrettable contingency, by all means familiar to the biologist.

A publication by Alizon and Montagnier[13] set an end to such speculations. The structural analysis of the two genomes ha by that time advanced sufficiently to allow a direct comparison between them. The differences between them were not of a magnitude to be explained by mutations. It was rather a matter of a complete restructuring, the disappearance of important structural parts and the emergence of new gene groups (fig.1 (1. A change from the HTLV-I to the LAV/HTLV-III (we have to give this name to the new virus, until a new nomenclature commission will decide on the priority between Montagnier and Gallo) could not have come about by a natural way known to the biologist. Alizon and Montagnier leave no doubt in this connection, stating that "this raises the question concerning the origin of the virus and the cause of the recent emergence of AIDS with all emphasis." The AIDS virus, accordingly, must be an artificia product, the result of a gene-manipulation.

During recent years our knowledge of the structure of the genom, the actual genetic substance of the viruses, greatly advanced, and contradictions between the various authors were largely cleared up. In the following we shall therefore report on substantiated facts.

All viruses of interest to us in connection with AIDS belong to the <u>retrovirus</u> family; their genome consists of a strand of ribonuclein acid (RNA), but it transcribed into a double strand of desoxyribonucleinacid (DNA) after penetration the host cell. The transcription thus takes place in a reversed direction from that to which we are accustomed in genetics,

a 5'carbon and ends with a 3' carbon. A series of genes is grouped at the end of the 5'carbons, belonging to the core, the carrier of the genome (gag=genome associated genes). They are almost identical in different retroviruses. This is followed by a group of genes coding the enzymes of the virus. The predominant role is here played by the polymerases, the enzyme forming the polymeric copy in the transcription. That part is therefore called pol. Here again there are great similarities between the different retroviruses. Section env codes the protein of the envelope. They are particularly important, since an immune serum the production of which involves work at numerous laboratories, must above all be directed against these proteins. Here great differences exist between LAV/HTLV-III and HTLV-I. These become even more marked in the following section. In HTLV-I there is a gene pair, to begin with the part recently called tat (transactivator) which codes a protein which increases the gene reading and thereby the virus production by about 100 times (Hazeltine et al.[15]). This is followed by section pX which codes a protein as yet unidentified (therfore X), which, however, is already known to transform a normal cell into a tumour cell. In LAV/HTLV-III the transactivator function is distributed to the two groups Q and F, with an acceleration factor up to 1000; a pX section is missing, which is comprehensible, since the AIDS virus does r transform the T4-cells into tumour cells, (Figure 1).

The direct comparison of the genomes can today be undertaken by three very reliable ways.

1. The sequence of different nucleotides in the genome can be ascertained. Largely concurrent findings from at least four laboratories are available for the same kinds of virus (Alizon et al.[16], Seiki et al.[17], Muesing et al.[18], Ratner et al.[19]). The sequences of various retroviruses may therefore be directly compared.
2. The genom is cut by appropriate ferments, the individual pieces are inserted in the genomes of other viruses or bacteriophages and the proteins coded by them are immunologically compared.

3. If a RNA-genome is transcribed into a DNA-double strand, the two DNA-single strands fit exactly to each other and therefore hybridise with each other. If the two single strands originate from two different viruses, only the genome parts which are very similar will hybridise. This becomes particularly apparent in the so-called heteroduplex-electronmicroscopy. For this purpose the two strands of different origin are built into a gap of a bacteriophage genome and examined under the electronmicroscope. The two DNA strands of the bacteriophages hybridise and form a thick double strand. The two heterogeneous strands remain separate, except for the places were a great similarity of genome prevails and where they hybridise, thus forming a thick double strand.

All three methods yield similar results. We shall therefore be confined to the presentation of the particularly evident results of the heteroduplex method (fig.2). In the experiment of Gonda et al.[20] presented here, whole genomes of different retroviruses were implanted into the genome of a bacteriophage. In fig. 2b the genomes of HTLV-I and Visna viruses are contiguous. They only hybridise near the 5'end in two small zones, marked by arrows, in the gag and pol ranges, which hardly account for 3 per cent of the whole genome.

Fig. 2a shows the hybridisation between HTLV-I and LAV/HTLV-III. There is a new range of hybridisation to be noted besides the two shown in fig. 2b (third arrow); it comprises about 3 per cent of the genome, i.e. roughly 275 nucleotides. In this case at least 50 per cent of the nucleotides must be matched.

The hybridisation between Visna and LAV/HTLV-III takes an entirely different course (fig.2c). The ranges of hybridisation are evenly distributed over the entire lenght of the genomes, making up altogether 35 per cent of their lenght. To investigate in how far coincidental conformities can simulate hybridisation, the LAV/HTLV-III strand was implanted in a reversed direction in a further experiment (fig.2d). In that

case there is no hybridisation at any point, which indicates that the relations demonstrated in fig.2c are not conditioned by coincidence.

It is therefore clearly shown that in the main part of their genomes Visna and LAV/HTLV-III are largely in conformity. The differences may well lie in the magnitude of mutations. On the other hand in this part of the genome LAV/HTLV-III fundamentally differs from the genome of HTLV-I. It is therefore completely excluded that the HTLV-I should of itself have changed, by an unfortunate combination of mutations, into the AIDS virus LAV/HTLV-III.

One might well be tempted to reverse Gallo's original hypothesis and to assume, that the Visna virus spontaneously changed into the AIDS virus. Yet, so far no scientist has gone as far as that conclusion - for a very good reason. By a coincidence - or a series of coincidences - a genome part of 275 nucleotides from the Visna virus would have had to change so greatly, that at least 50 per cent of them fitted to the corresponding section of the HTLV-I genome, since it is common to the HTLV-I and the HTLV-III, as shown above. The probability that this might happen is $1{:}6 \times 10^{82}$. Such an event is therefore absolutely impossible, and corresponding results will also be obtained, if, instead of hybridising the genomes, their nucleotide sequences are compared with oneanother. There could not have been a coincidental, spontaneous transition from Visna to AIDS virus.

The 5'end of the genome therefore originates from HTLV-I, its larger part with the 3'end from Visna virus. The whole thing is a "chimera", a system of two components of different origin, artificially by nature and only brought by the skills of genetic engineering.

Recently the nucleotide chain of the Visna virus has been sequences (Sonigo et al.[21]). On that basis Stephens et al. [22] drew up a phylogenetic tree of the retroviruses. According to this, the LAV/HTLV-III are very closely related. A branch far remote from them comprises HTLV-I, HTLV-II, BLV (bovine leukemia virus) and other animal viruses. The marked [illegible] between HTLV-I and LAV/HTLV-III is

also demonstrated by the phylogenetic trees drawn up independently by Chiu et al.[23], Wayne-Hobson et al.[14], Gonda et al.[24] and Watanabe et al.[25] (fig.4). A spontaneous transition from the sub-family HTLV-I to the sub-family HTLV-III/Visna must be completely excluded biologically.

This revelation, that the AIDS virus is a chimera created only a few years ago, both parts of which have not yet had time to co-ordinate with each other, explains an important phenomenon, the effects of which may perhaps prove to be tragic. Whereas HTLV-I, HTLV-II, Visna and the other retroviruses investigated in this connection show genetic stability and only a few mutations, the genetic behaviour of the AIDS virus is dominated by numerous mutations. We already mentioned that the genomes isolated by Montagnier and Gallo from viruses of AIDS patients from the American East coast differed from oneanother by approximately 1 per cent, but the viruses isolated a year later by Luciv on the West coast deviated from them by as much as 5 per cent. Subsequently the mebers of the Montagnier group isolated from different patients independent LAV strains, and they all greatly differentiated from oneanother, except if two strains were isolated from the same patie

A similar instability is also observed in the effect of restriction enzymes (e.g. Shaw, Gallo et al.[26]). These are enzymes, which cut nucleotide chains, i.e. genomes, at certain defined points. This has made them a reliable scalpel in genetic engineering. In all cells or viruses so far examined the restriction points are genetically determined and extremely stable. Different isolates of HTLV-I or -II are fully identical in this respect. In LAV/HTLV-III however, the restriction points very almost in each patient. Similar to the frequency of mutations, this behaviour also goes to show that the AIDS virus constitutes a combination of two unco-ordinated genome components artificially joined by means of genetic engineering. It could hardly be assumed that a system with such a marked genetic instability should be the result of a biological evolution.

Specialist circles hope that the first vaccines against AIDS will be available by 1990. This vaccination will be directe

from the exterior. If these have in the meantime come to form numerous variants by mutation, there will be many virus strains against which the vaccination will only have a weak effect or none at all, or a vaccine protection adequate to begin with will rapidly weaken to the extent in which new mutants develop, and frequent subsequent vaccinations with new vaccines will become necessary. This is presumably the most serious problem facing the combat against AIDS in the coming years.

Gene manipulation

Gene manipulation of pathogenes entails grave danger to the population and is subject to strict legal regulations. In particular, a P-4 type laboratory is required which should exclude all leakages pf pathogenes. The first laboratory of this kind in the USA - presumably in the whole world - was installed at Fort Detrick, Maryland, in building 550, in 1977 (Piechocki[27]). Fort Detrick had for a long time been the central laboratory of the Pentagon for the development of biological agents of warfare. When an international agreement was signed in 1972 which prohibited the development, possession and transmission of such agents, the establishment was officiall converted into a research centre for immunological defences against infections. Yet the construction of a special laboratory for gene manipulation clearly shows that the original objectives had by no means been abandoned.

It may be assumed as a matter of course that the techniques of gene surgery had been tested with non-infectious material even before the opening of P-4 laboratory. Accordingly the first products of gene manipulation of pathogene germs must have been available at the end of 1977.

In Fort Detrick it was by all means customary to make use o voluntary test persons for experiments with the pathogenes: persons sentenced to long terms of imprisonment, promised remission in case of survival. Up to 1969 423 cases of disease among test persons with 4 deaths were registered at Fort Detrick. At the end of 1977 the first test person were probably infected by manipulated pathogenes from the P-4 laboratory, including

in this case is between 1 1/2 and 2 years. After 6 or even 12 month no serious symptoms were registered, apart from cases of apparently harmless lymphadenopathy; the newly created pathogene was regarded to be inadequately effective and the test persons were released.

Criminals who had engaged in homosexual practices during the long time of their imprisonment obviously concentrated in the nearest big city after their release; it is therefore logical that, after the end of the incubation period, i.e. about 1979, the first AIDS cases should have been registered in New York, to begin with exclusively among homosexual men.

This is, to begin with, a hypothesis, a chain of circumstantial evidence, but it stands up to critical contemplations. If a military objective sets up a special laboratory for the manipulation of pathogenes, it must be concluded that the intention exists to conduct gene manipulation of germs and we may be certain that pathogenes manipulated in this way are being produced, reproduced and stored. AIDS was a failure; the really existing and undoubtedly devastating material is something we can only guess.

We have seen that the AIDS pathogene is likely to result from a gene surgical combination of the HTLV-I and the Visna virus or forms very similar to these. Who, if not the military, should come to think of coupling the pathogenes of two deadly and incurable diseases? And if the disease, with an incubation period of two years should break our about two years after the opening of the P-4 laboratory at Fort Detrick, in the immediate vicinity of that laboratory, for the first time, there could hardly be any doubt about the fact that the manipulation was conducted namely there.

The only hypothetical factor is the way in which the virus emerged from the protected laboratory. We offer a plausible explanation, which we can substantiate by a qualified argument. AIDS to begin with appeared exclusively in circles of homosexual men, which was subject to a great deal of guesswork. Next there were the wives of drug addicts, jointly using an unsterile needle, women infected by blood transfusions, women

of prostitutes. Specialists speak of a break-out of AIDS from the confinement to homosexuals. In Zaire (Equatorial Africa), where homosexuality and drugs by tradition played an insignificant role, the proportion of AIDS patients even at this point is 1.16 : 1 between males and females (Mann et al.[23]

It is eveident, therefore, that AIDS is not a men's disease and even less of homosexuals. Had the pathogene been brought to the USA from outside, it would have evenly multiplied among both sexes. The fact that to begin with AIDS only became prevalent in circles of homosexuals shows that the pathogene at first only became effective in conditions where it could only reach homosexual men, which was among test persons at Fort Detrick.

Epidemiology

The first 4 AIDS cases were reported to the health authorities by the New York physician Dr. Gottlieb in 1981. After this became known several other cases of disease were soon identified as AIDS. Retrospectively a number of diseases registered in 1980 and one or two cases of 1979 were also recohnized as AIDS, all of them in New York. Approximately a year later AIDS appeared in San Francisco, the centre of American homosexuals, another eighteen months later also in Chicago. AIDS therfore first appeared in New York in 1979 and from there spread out over the USA (L'age-Stehr[29]).

Outside the USA AIDS became noted at a later time. In Western Europe the first cases were reported in 1981 and 1982. (L'age-Stehr[30]; Rao et al.[31], Bartholomew [32]). In South Africa and Trinidad the first AIDS cases were described in 1983, in Japan the first LAV (not yet full-blown AIDS) was found in 1984; Okinawa does not seem to have been effected by AIDS up to 1985 (Tsuchio et al. [33]).

In many cases the primary infection may be traced back to the USA. In the FRG the first 6 AIDS patients were registered in December 1981. Mehlmann et al.[34] commented in this connection, that most of these patients had "numerous and internationa contacts, in particular with homosexuals from New York"; they

first two AIDS patients from South Africa, both white homosexuals, had visited the USA prior to their infection (Raz et al.[31]). From Great Britain there is convincing evidence of the fact that haemophiliacs treated with English preparations had been free of AIDS at least up to 1984, whereas others receiving American stored blood units in many cases showed positive serum reactions (Moffal and Bloom [35]). Melbey, Biggar et al.[36] established that AIDS was imported to Denmark and Australia by homosexuals who had spent their holidays in New York or San Francisco. Tsuchie et al.[33] found no antibodies against the AIDS virus in homosexuals or drug addicts in Japan, but identified it clearly in hemophiliacs who had been treated with Factor VIII od IX of American origin. Harfi and Fakhry[37] stat that AIDS was unknown for a long time in Islamic countries. In Saudi Arabia there were two cases in 1984, one adult and one child. Both had been treated with blood units of American make.

Franceschi et al.[38] compared the frequency of AIDS-positive sera of two north Italian districts, Udine and Pardenone, with equal numbers of inhabitants, similar climatic conditions and similar demographic structures. Pardenone, however was found to have 8 times as many positives sera as Udine. In Pardenone there is an American air base.

The centre od the dissemination of AIDS was obviously in the USA. This is only called in question in regard to the countries of Equatorial Africa. We shall discuss this important aspect in a separate chapter.

Wherever the epidemic appeared the number of cases roughly doubled within 6 months. Improvement was only achieved after an extensive campaign of enlightenment had informed the groups at risk about the possibilities of a less dangerous way of living together, and after stored blood had been sterilised by heating up.

The World Health Organization (WHO) noted in its report of November 1985, that the doubling period had increased from 6 to 9 or 10 months, expressing the hope that in the near future the frequency of cases would not double before a period of 12 months.

In the meantime the situation has remained grave. An effective therapy is as yet unknown, at best the treatment of individual opportunistic infections allows some slight delay of the fatal end.
So far, however, every patient suffering from full-blown AIDS has died.

The hope remains that an effective protective vaccine against the virus can be developed, but all experts agree that this could not be expected before 1990, and even then it would have to be seen in how far the vaccine was effective in view of the numerous mutations of the genome.

Let us make the optimistic assumtion that we had found an absolutely effective vaccine by 1990 and the means to apply it universally. Hoping that the period of doubling frequency would, in fact, be extended to 12 months, we could make the following prognosis. In the USA there were 12 408 AIDS patients on August 12th, 1985. By the end of 1985 there would be more than 15 000. During the 5 years up to the use of t. new vaccine there would be 480 000 patients, all of whom would b. doomed to die within one to three years.

Unfortunately this is not the end of the tragedy. In the mass media AIDS was repeatedly compared to an iceberg of which only the tenth is visible above the water surface. The comparison fits precisely. A large number of apparently healthy persons is infected by the AIDS virus. In many cases the infection takes a course without symptoms, or merely leads to a harmless lymphadenopathy; only in one tenth of them a full-blown AIDS is developed. In November 1985 the WHO estimated the number of these virus carriers in the USA alone at 800 000. With a doubling period of 12 months, there would be 25.6 million virus carriers by the end of 1990, which would mean that there would be 2.56 million AIDS patients for whom vaccination would come too late. These figures make even the bomb victime figures of Hiroshima appear insignificant.

Possibly this projection will prove to be too optimistic. We already mentioned that the AIDS virus contained a large part of the genome of the Visna virus which causes serious

indicate that it may affect the central nervous system also in humans (5,6,7). Incubation periods last 4-15 years. If the lymphadenopathy healed up 2 to 3 years after the infection, without the disease developing into full-blown AIDS, the patient was considered as cured, which happened in 90 per cent of all cases. Yet it was observed that years later such patients contracted a brain disease so far incurable. At the National Cancer Institute in Bethesda, USA, a group of persons has been under observation since 1982, who had been exposed to the AIDS virus. So far, as made known by Fauci, staff member of the Institute(39), approximately one third of th group has fallen ill with AIDS, and a receding trend is not noticeable in the number of cases. Fauci reckons that the number of diseased will not reach 10 per cent, but 40 per cent of those infected.

There was a danger of popular mass protest against the preparation of biological warfare. This explains why the media, which had at first operated with prognoses of approximately 5 million patients, for purposes of sensation mongering, suddenly screwed back their estimates to a mere 2 to 300 000 patients, "to avoid panic".

Nor were the experts able to ignore the problem. At the meeting of the American Association for the Advance of Science (AAAS) in June 1984 (Smith(40)) many participants spoke about th dangers to mankind entailed by the opportunities for gene manipulations in military laboratories. The AIDS problem was not directly mentioned. It should not be forgotten that our knowledge of the structure of genomes was then not adequate to supply the clear evidence of the development of the AIDS pathogene by means of gene manipulation, which we can do today.

A further reaction on the part of biologists was called forth when the Pentagon applied for the means to set up a new P-4 laboratory, this time at "Dugway Probing Ground", a military testing site in the state of Utah. The possibilities of the spreading of pathogenes, in particular viruses, by aerosols were to be experimentally tested there. Finally

such as Bob Durban and Richard Novick produced evidence to show that the envisaged institution could only serve the testing of new pathogenes, i.e. purposes of biological warfare (Smith[41]).

The legend of the green monkey

In this tense situation Max Essex released his legend of the green monkey. We expressly say "released", because Essex did not published his ideas in any scientific journal known to us. They appeared on television and in magazines, processed by moderators and reporters, but without a single authentic sentence by the author. As far as we know, Essex presented his opinion to circles of scientists only on two occasions, the first time at the First International AIDS Congress in Atlanta (USA) in the spring of 1985, yet without as much as printed summary of his statement in the Congress documents; the second time was at a Symposium on "AIDS in Africa" in Brussels, in November 1985, where he submitted a text of one page and presented a poster. We have to refer to this document, since Essex, contrary to scientific usage, did not supplement his Congress statements by scientific publications.

We also consciously chose the term "legend". A legend may be believed or not, it is not based on fact and does not attempt to prove anything.

This is the story: Essex and his associates (Kanky et al.[42,43]) examined a group of 104 healthy green monkeys in Central Africa, living in freedom (green long-tailed monkeys - ercophitecus sabaeus). In 57 per cent of all test animals they found a retrovirus, eveidently not pathogenic. It showed certain cross reactions with some proteins of the LAV/HTLV-III of the 5'end of the genome, which is not surprising since we know that proteins of the gag and the pol ranges are similar in all retroviruses. There was no investigation of the other genome parts, and on this dubious basis Essex explained that the monkey virus had been transferred by way of wounds inflicted by bites and scratches, causing AIDS, the

The mass media even reported that the two could hardly be distinguished.

In evidence it was stated that the monkey virus could also be found in healthy Africans (figures of about 90 per cent were given). To prove that the monkey virus caused AIDS in humans it was stated that in 17 out of 32 carriers of LAV/HTLV-III in the USA (53 per cent), simultaneously with it, the monkey virus had been serologically proved.
In AIDS virus carriers in Zaire that proportion was said to have been significantly greater.

This is too great a strain on logical thinking. The monkey virus is alleged to act as an AIDS pathogene in humans, or to transform into the AIDS pathogene, and at the same time examples are given of healthy Africans with a positive serum reaction to the monkey serum. The monkey serum is said to call forth AIDS in humans, but in 53 per cent of the cases it peacefully coexists with the alleged AIDS pathogene, evidently without causing any disease. And if 53 per cent of the American virus carriers owe their disease to the monkey virus - where did the remaining 47 per cent contract their AIDS?

The assertion that both viruses were extremely similar, if not identical, is equally absurd. Essex can serologically identify both viruses a part within the same patient; they therefore have at least in part different antigenes, they are thus composed of different proteins. They can therefore not possibly cause the same disease.

Without making mention of the legend of the green monkey, the World Health Organization made explicit statements on this question in its epidemiological report of 1985[44]. We can read there, about the T-lymphotropic monkey viruses: "some of these viruses have insignificant relations with the LAV/HTLV-III viruses of human origin." A WHO report does not reflect the personal opinion of an individual, but the view of a panel of the best specialists. How did the WHO arrive at its conviction?

In the autumn of 1984 and in the spring of 1985 two works appeared by a Japanese research team, including well

(23,95)

They cultivated virus strains from 5 kinds of monkeys (3 Japanese rhesus monkeys, the green monkey and the chimpanzee from Africa), which they compared with different strains of HTLV-I. They used the methods of hybridisation and the direct comparison of genome sequences. Both procedures yielded corresponding results.

All isolates of the HTLV-I proved to be almost identical, with deviations of less than 1 per cent. The 5 monkey viruses showed almost the same close affinity with oneanother. They all also showed astonishingly good conformity with the HTLV-I, with differences in all parts of the genome of only about 10 per cent. Fig.3 shows the sequences of the 3'genome end in HTLV-I and in the virus of Macaca nemestrina rhesus monkey. Bracketed - the ranges corresponding in both genomes, outside the brackets - the deviations, in this case exactly 10 per cent. This range was selected, because we know that it has no conformity at all with the LAV/HTLV-III.

On the basis of these results, the Japanese authors drew up a phylogenetic tree of HTLV-viruses. Fig. 4 shows that the different STLV-viruses (S=simian, originating from monkeys) constitute a closely related group, which for its part is closely related with the HTLV-I. The HTLV-II and BLV (bovine leukemia virus) derive from the same branch. They all originate from a common ancestor-virus, up to now unknown, from which the AIDS virus must have developed independently of it. This excludes all chances of the STLV having transmuted into HTLV-III on transfer to humans.

The virus of the green monkey, therefore, is closely related with the HTLV-I and has no relations at all with the AIDS pathogene. The legend of the green monkey should not have been allowed to arise; Essex, as virologist, should read the well known and widespread journal "Virology", and if not, he could have heard from his colleagues about the work of the Japanese research team. As it is, it becomes clear that there were good reasons why the assertion of Essex have not been published in any scientific journal, and why we find no reference to them in any scientific contribution by his professional

public, feeling threatened by the spreading of AIDS; the attempt was successful.

The facts to retain are confined to the finding that the green long-tain monkey of Central Africa was contaminated to 50 per cent by an apathogenic virus (not causing disease), and that this also applied in regard to the North American human population and, perhaps to a slightly greater extent, also to the African human population. We were introduced to a similar case in the cytomegalovirus, which is a parasite of the adult population in proportions varying from one country to another between 40 and 100 per cent.

Nor could the prevalence of the virus in humans and monkeys astonish us. Mixed virus reservoirs are frequent. Rabies viruses for instance may be present in humans, dogs, deer, etc.

The "AIDS-explosion" in Africa

Even without the green monkey some scientists hold that AIDS had existed for a long time in Equatorial Africa in an endemic form, having assumed an acute form at the end of the seventies; it is alleged to have been exported to the USA and to have spread from there to the rest of the world. Two arguments are advanced in support of this theory. Firstly, sera, collected decades ago for other reasons, had been found to have cross reactions with the AIDS pathogene, which might speak in favour of the existence of LAV/HTLV-III prior to the year 1979. We shall deal separately with this argument in the following chapter.

Secondly, the AIDS epidemiology in Central Africa is presented as an explosion, indicating that the population there is particularly receptive for AIDS, being predisposed for the development of the new disease. The virus had, to begin with, been apathogenic, i.e. it had been suppressed by the natural forces of resistance, but had presumably overcome these forces, probably as a result of advancing urbanisation. Strangely it is emphasised in particular, that there was reason to assume that African AIDS was of a specific nature. It did not show the

This latter argument may be discussed as unsubstantiated. In Central Africa homosexuality is hardly prevalent, and parenteral drugs are too expensive for a large section of the population, so that "fixers" could hardly form a significant risk group there. AIDS was presumably imported to Central Africa not by way of homosexuals, but in stored blood, so that it affected men and women to an equal extent.

Nor can we believe in the harmful effects of urbanisation as a factor weakening the natural forces of resistance in humans - in contrast to some radical oecologists. In Africa urbanisation means drinking and washing water free of parasites, an hygienic disposal of waste water and garbage, food with more proteins, better medical care, and above all reduction of the frequency of the numerous diseases caused by infection and parasites which seriously burden the forces of resistance of humans, particularly in tropical regions. How should all this destroy any existing immunity against AIDS? And why did urbanisation, a process which has continued over decades, effect that transition namely at the time when a P-4 laboratory in Fort Detrick took up its work?

Then there would be still the question as to why a type of AIDS developed in Central Africa should prove to be particularly virulent. Remnants of previous immunity should have been preserved and effect a reduced susceptibility. Logically an increased susceptibility rather indicates the pathogene is an entirely novel type for the population of that region. A contrary conclusion would be absurd.

None of these authors deals with the problem as to why a pathogene originating in Africa should systematically and exclusively expand towards New York; and there can be no doubt that the further prevalence departed from that city. In the colonial era contacts with the European mother country were very close. European officials, technicians, plantation overseers and military came to the colonies, coloured soldiers were transferred in large numbers to Europe, as politically reliable security troops, and the large number of half-castes testify for sexual contacts between both sections. Even after

colonial rulers remained more intense than with the new business partners from the USA, all the more so since in France, for instance, there were no social nor sexual prejudices against black Africans. If AIDS had in the first place originated in Africa, it would certainly not have made its way into the world via the USA, but via Europe.

We need to examine the question, as to whether the alleged AIDS explosion in Central Africa does in fact correspond to reality. Let us begin by taking a look at conditions in Kinshasa, the capital of Zaire, frequently described as African AIDS inferno.

According to Mann et al.[28] there had been approximately 30 AIDS cases at the beginning of 1985 to 100 000 inhabitants; 10 per cent from outside, and thus 27 patients from Kinshasa. Frank et al.[46] mention figures of 17 - 20 : 100 000, Piot et al.[47] estimate 17 : 100 000 in 1984 and more than 30 : 100 000 for 1985. A WHO report of September 1985 estimates figures of 17 - 40 : 100 000. Roughly 30 AIDS patients to 100 000 inhabitants of Kinshasa appear to be a probable mean value.

Comparing the AIDS frequency of San Francisco, as one of the USA cities with a high AIDS concentration, estimated figures also vary to some extent, but if the earlier WHO figures are extrapolated to the autumn of 1985, the figure will approximate 380 : 100 000.

The following consideration will lead to a somewhat lower estimate: in the summer of 1985 one AIDS patient died every day, and two new cases were registered. Roughly 730 inhabitants a year fell ill, and as an AIDS patient lives for 2 years on the average, there were presumably 1,460 patients in the city at that time. With a population of 720 000 this would approximate a proportion of 202 : 100 000.

The first figure comprises the living and deceased AIDS patients, the second figure only those surviving at present. These figures by no means contradict each other. The figure of 300 : 100 000 should correctly reflect the situation. If this is true, the number of AIDS patients in San Francisco is ten time

Similar figures will also be found in regard to AIDS contamination in the USA and Europe. According to the WHO there were 12,408 AIDS patients in the USA up to August 12th, 1985. In the states of Western Europe 940 cases were registered up to March 1985, which extrapolated to August 1985, should correspond to approximately 1,200 cases. The frequency rate between the USA and Western Europe, with roughly the same number of inhabitants, is therefore 10 :1.

We also learn from a WHO report, that the number of AIDS virus carriers in the USA is estimated at 800 000. The corresponding figure for Western Europe is 80 000. Here again the proportion is 10 : 1.

This difference is explained by all specialists by the circumstance, that in Europe the prevalence of AIDS set in with a delay of 2 1/2 to 3 years as compared to the USA. If Central Africa shows roughly the same difference to the USA as Western Europe, it is estimated that the prevalence of AIDS set in there at about the same time. This can be substantiated by numerous clinical reports, of which only a few examples will be quoted:

Kalata [48] reported from the Lumbashi hospital (Zaire) on AIDS cases admitted in December 1982, in March, April and December 1983 and in February to June 1985 with cryptococcus meningitis. 7 of them had all symptoms of full-blown AIDS. As far as we know the case of December 1982 is the first documented AIDS case in Central Africa.

Mazebo et al.[49] reported on 93 patients admitted to Kinshasa University hospital between 1983 and December 1984. Cases before 1983 were not mentioned.

An investigation extended over long years by Bayley et al.[50] on the prevalence of the Kaposi sarcoma in connection with AIDS is particularly revealing. Like other authors, he differentiates between the "typical", relatively benign KS, which is easy to distinguish from the "atypical" virulent KS frequently found in AIDS patients. The typical KS is endemic in Zambia, Uganda and Kenya; the author registered an average admission between 8 to 12 cases a year over several years.

This figures remained almost constant up to 1985. As from 1983 however, there was an increasing frequency of cases of atypical KS. During the first 4 months of 1985 there were as many as 21 cases, which, extrapolated up to the end of 1985 would correspond to 63 cases. (table 1). Parallel to this the first cases of the "AIDS related complex" (ARC) appeared in 1983, which increased at a corresponding rate during the following 2 years.

Table 1 Distribution of new cases of KS and AKS in Zambia

Typical KS		Atypical KS	
before 1983	8 - 12	before 1983	0
1983	10	1983	13
1984	15	1984	22
4 months of 1985	(4)	4 months of 1985	(19 + 2 children)
12 months of 1985	12	12 months of 1985	approx. 63

Here we recognise clearly two symptoms of disease independe of each other; one endemic, constant, typical KS, and an atypic form which appeared as from 1983, at about the same time as ARC, with the LAV/HTLV-III infection, the frequency of which increased logarithmically.

We know of no hospital report which mention AIDS cases of the time before 1982. At this point we wish to counter the argument, that in the primitive medical conditions in Central Africa it should easily be possible that rare individual cases were never brought to the knowledge of physicians.

Even in the colonial days the governments had installed excellent hospitals in the tropic cities, if only for the sake of their own protection, which in particular watched the prevalence of tropical diseases with great care. In the French and Belgian colonies there were also departments of the Pasteur Institute of Paris at work in the colonies, which intensified their activity after the liberation with the suppor

At least in the environment of the main centres no case of AIDS would have escaped their attention, concentrated on tropical diseases. If no AIDS cases were registered in clinical reports before 1982, we may be sure that this reflect the true state of affairs.

Literature is again and again haunted by the same 4 cases, in which it is alleged that AIDS had been found in Africa at an earlier time. We shall quote one example:

Jenkins et al.[51]: an English woman, white, 49 years old, fell ill with AIDS in May/June 1984, with opportunistic infections and positive serum reaction to LAV/HTLV-III. In 1979 she had sexual relations with her husband, a black man from Ghana, who was completely healthy. Nevertheless, the authors assume that the husband had been a virus carrier without symptoms, and that AIDS had existed in Ghana in 1979. They are not troubled by the fact that the incubation period would in this case have had to extend over 4 1/2 years, nor do they consider the possibility that the patient might have been reluctant to admit subsequnet sexual contacts.

Recognition of the fact that AIDS appeared in Central Africa at about the same time as in Western Europe was also expressed in the WHO report of November 1983 [52]. To begin with it deals at length with the situation in the Caribbean and notes that most AIDS cases were notified since the beginning of 1982. As to Central Africa the first cases were only mentioned in 1983. We may therefore feel quite justified in our assertion.

Immunological problems of AIDS in Africa

In apparent contradiction to this there is the assertion by several prominent scientists to the effect, that they found a large number of positive reactions to LAV/HTLV-III antibodies in serum samples of the years 1980 and even 1970. Such serum samples were collected from representative population groups within the scope of epidemiological investigations, e.g. of B-hepatitis, and the rest was preserved mostly by

The contribution by Saxinger et al.[53] is generally quoted, in which 75 sera of children were investigated in the years 1972 to 1973. 50 of them, i.e. 66.6 per cent, proved to react positively to LAV/HTLV-III. The average titer of 601 lies on the treshold of provability.

Sera collected in East Africa, Uganda, Tanzania, Kenya and West Africa (Ivory Coast) also date from the beginning of the seventies. 40 per cent of these sera were proved to have positive reactions to LAV/HTLV-III (De-Thé et al.[54]).

The oldest serum samples we know originate from Kinshasa, of the year 1959; they were investigated by Nahmias et al.[55]. Out of 672 samples only 64 proved clearly negative (ELISA-cutoff 1). 591 sera had 1-3 ELISA-cutoff and were therefore borderline cases. 15 sera had 3-7 cutoff, i.e. weakly positive, and 2 were clearly positive with 7 cutoff. Here more than 90 per cent of all sera thus proved to be more or less AIDS suspicious.

Such results, to which we could add many more, give rise to questions. With a contamination of 50 per cent a large scale frequency of AIDS should be noted among approximately 5 per cent of the population after about 2 years, and about 2 years after that there should have been a correspondingly large number of deaths. The reactions of authors vary. Some assume that this was not the genuine LAV/HTLV-III, but a "prae-AIDS virus" not yet pathogenic; others consider that it might possibly have been a cross reaction with an apathogenic virus not having any relationship with AIDS.

Brun-Vézinet et al.[56] also consider that perhaps these results might have been "false - positive" values, particularly frequent in the ELISA-procedure. We shall go into this question in greater detail presently.

These results become even more dubious in the light of an investigation by Rodriguez et al.[57]. He investigated serum from 4 Indian tribes of the Amazons region, having very little contacts to whites. The sera were of different ages, some of them older than 16 years, and they showed between 3.3 to 13.3 p. cent positive relations to LAV/HTLV-III, according to tribe.

The titers were very weak, on an average 128, 60, 200 and 129. With the same testing substance Rodriguez received titers of 2560 from two bleeders. Since it could hardly be assumed that AIDS should have developed independently in Central Africa and in the Amazon region, Rodriguez considers that this was an apathogenic virus with a cross reaction to LAV/HTLV-III.

It is particularly strange that, since the appearance of AIDS in Central Africa the contamination of the population should have been greatly reduced. Instead of 40 per cent and more, Zugury, Lachune and Gallo [58] found 6.7 per cent positive sera, Brun-Vézinet et al.[56] state only 5 per cent for the population average, even in the AIDS concentration centre of Kinshasa. Even among men with numerous contacts with prostitutes Brun-Vézinet et al.[60] found less than 1 per cent positive sera in 1980 (the unprecise data even point to the prevalence of false-positive values).
In 1983 the AIDS positive sera had increased to 13 per cent. All this is far less than allegedly found among a predominantly rural population before the outbreak of the AIDS epidemic. How could this marked decline in AIDS contamination be explained?

A first indication may be taken from an information by Desmyter and Montagnier [61]. They wrote about their experiments with long stored serum: "Our work on the anti-LAV was disturbed by a stickiness which appears especially in old sera and could lead to the wrong conclusion that the anti-LAV antibodies had been more prevalent in 1970 than in 1980". In other words, the older the sera, the more false positive values were measured.

This question was closely examined, among others, by Segal and Segal [62]. By partial denaturation of the side chain bridges in its protein molecule the antibody loses affinity and avidity. It reacts less intensely than the native, and binds itself to antigenes with a deviating structure. This behaviour, for example, is depicted in fig. 5a and b.

This kind of denaturing takes place particularly easily in

and with them also the hydrate envelopes which stabilise the side-chain links (Ismailova and Rebinder[63]). After this hydrophobic side chain bridges frequently break up even at room temperature.

The specific properties of antisera are more effectively preserve by deep-freezing. It appears that they can be preserved indefinitely at -20°C. In inadequate cooling, such as during transportation on ice, denaturation sets in after days.

Fig. 5 illustrates the conditions in well and badly preserved serum. We depart from the assumption that, according to Essex, about half of all human beings, even if in good health, are contaminated by an apathogenic virus, which is also found in the green monkey. In Central Africa, according to Essex, this applies in 90 to 100 per cent of all cases. Fig. 5a illustrates a serum with antibodoes against LAV/HTLV-III and against the apathogenic STLV virus. The range of reaction of the very selective Western blot is entirely situated within the specificity range of the LAV, that of the somewhat less specific ELISA test reaches somewhat further, without attaining the specificity range of the STLV antibody. Both tests show a powerful reaction to LAV.

Fig. 5b shows the situation in a healthy human being. Antibodies against LAV do not exist. Antibodies against STLV should be contained in many, if not all sera, but their specific properties are outside the reaction of both tests: the serum is negative.

If the serum is preserved by lyophilisation, the situation is as presented in fig. 5c. The specific range of the STLV antibodies is widely smudged, reaching the reaction sphere of the ELISA and also that of the Western blot. The latter is particularly important. The results obtained from old sera, doubted not only by us, were repeatedly explained by the fact, that the tests, particularly the ELISA test, tend towards false reactions. The results were therefore checked in several cases with the costly but extremely reliable Western blot test and they confirmed the ELISA measurings. This does not mean that the positive reaction was caused by LAV antibodies, only th

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This explains all observations. Fresh serum, or serum stored at low temperatures prove to be negative, in as far as there are no LAV antibodies in them. This possibly explains that a group of sera from various regions of Africa, collected before 1980 was proved completely free of LAV/HTLV-III antibodies. The authors, Schmitz and Kern[67], had preserved them at -20°C.

As a counterpart to this we quote the work of Biggar et al.[65]. In the remote djungle region of Kiwu in East Zaire, 250 serum samples were obtained from out-patients. 31 of them (12.4 per cent) were LAV positive, but with very weak concentrations (5.0 ELISA cutoff), and another 30 were borderline cases (3 to 5 ELISA cutoff). The serum had not been preserved for years, but in the djungle of Kiwu there were undoubtedly no freezers available, and the inadequately cooled sera were slightly denatured when they arrived at a central hospital.

It is noteworthy that in all samples of this kind, with apparently numerous LAV positive serum, the titer's are very low, mostly attaining only about 1/10 of the normal reaction and largely situated in the sphere of uncertainty. Data on the titers will be found in the above mentioned contributions by Saxinger et al.[53] (Titer 601, on the border of provability by Rodriguez et al., average of titers 120, normal titer 2560). Nahamias et al.[55] found 591 sera among 672 samples with an ELISA cutoff between 1 and 3, i.e. within the realm of uncertainty. With Biggar et al.[65] the values were also below 7 ELISA cutoff, mostly far within the border range.

On the other hand in the contribution by Zagury, Larhune and Gallo [58] already referred to, great care was taken of the good preservation of the serum. Thanks to a special agreement with the aviation company it was possible to have the samples obtained in Kinshasa investigated at a laboratory in the USA within 24 hours. Although the samples came from Kinshasa, a city particularly affected by AIDS, the number of positive sera of healthy control persons was only 3 to 5% (0.6 per cent

1) In this context we wish to report a paper submitted by a [65]

investigated two batches of sera from the USA; they originated from hemophiliacs, one was collected in 1954, the other even earlier. 94 per cent of the sera of 1954 displayed a positive reaction against LAV/HTLV-III, and even in the older sera the appearent prevalence of antibodies against LAV/HTLV-III reached 53 per cent. As we cannot suppose, that 30 years ago the AIDS virus had spread to nearly the whole population of the USA only to decrease suddenly to the present prevalence of 0.25 per cent, we must conclude that we are dealing with "false-positive" reactions, due to a loss of specificity during the long storage.

This effect is linked to a decrease of the strenght of reaction. Thus we understand, why, in the extremely old sera, part of the false-positive reactions could not be detected.

We feel entitled to conclude that the same might have happened to some sera collected in Africa during a storage of 10 and more years.

All these results fit without contradiction into a scheme shown in figs. 4 a - c. A confirmation of these ideas by an entirely different way is facilitated by the investigations of the reliability of the different test kits. Hunter et Menitore [67] and Weiss et al.[68] found in test kits admitted for medical use (without mention of the firm) up to 6 antibodies against antigenes originating from the T4 cells used for virus reproduction. They "showed only weak reactions with ELISA and were negative in Western blot". (Weiss et al.[68]).

Van den Acker and Hecker [69] investigated 15 sera of healthy staff members of the laboratory by means of the Abbott HTLV-III enzyme immunoassay (an ELISA-technique), licenced by the US Food and Drug Administration.
In accordance with the regulations, the serum was to begin with heated to 56°C for 30 minutes, in order to destroy the germs of disease. All sera proved to be weakly positive, with an ELISA cutoff between 1.2 and 3.1 and a mean value of 2.1, i.e. in the realm of uncertainty.

If the sera were not previously heated, contrary to the

between 0.2 to 0.7, means value 0.4.

These relations are illustrated in fig. 5d and 5e. In fresh sera the specificity range of the alien antibodies does not extend into the reaction range of the ELISA tests. The reaction is therefore negative (Fig.5d). If the material is slightly denatured by heating the specificity range is extended, overlapping into the reaction range of the ELISA test, but not into that of the Western blot, and in working to rule we receive a number of false-positive values only eliminated by the Western blot (Fig.5e).

This confirms our concept, according to which in fresh sera separate groups of antibodies are differentiated by the modern testing methods, whereas in partial denaturation - by lyophilisation, inadequate cooling, or moderate heating - "false-positive" values will be obtained, which, however, mostly do not surpass the uncertainty range.

We may therefore hold the view today, that the positive reactions repeatedly established in old sera to LAV/HTLV-III by no means prove the existence of that pathogene in Africa prior to 1980, and that the clinical findings, according to which AIDS appeared in Central Africa around the same time as in Europe, may be regarded as reliable.

Yet another circumstance needs clarification. In the USA the number of LAV/HTLV-III positive sera are stated to be 0.25 per cent for healthy persons. Yet we must mentioned that a research team associated with Gallo found 6.6 per cent positive sera, carefully preserved, coming from Kinshasa. This looks as though the African population was far more contaminated than that of the USA.

Yet it should be considered that Kinshasa is not representative of Zaire as a whole. Let us consider in comparison the situation in the USA. With a total of 220 000 000 inhabitants the figure of approximately 12 400 cases will mean an average of 5.6 cases to 100 000 inhabitants. For San Francisco, the main AIDS centre of the USA, we calculated a figure of approximately 300 : 100 000, i.e. 53.5 times higher than the national average. If in Kinshasa, the AIDS-centre of Zaire, contamination has

national average, which would be 0.12 per cent. In comparison Hunsman [70] stated a contamination rate of 0.16 per cent for the FRG at the beginning of 1985.
The contamination rate of Zaire, for which we could not find any results of direct statistical investigations, may be estimated by all means in line with figures relating to Western Europe. This proves, that there is no substantiation to assume a particular predisposition of the African population to AIDS.

An argument of quite a different nature is owed to an investigation by Kreiss et al.[71]. In Nairobi (Kenya) there are two categories of female prostitutes strictly separated by price levels. The cheaper category has exclusively native clients. It was found to be seronegative without exception in an AIDS-test. The xpansive category, which also serves European and American customers, was 50 per cent seropositive. The infection was therefore imported by the white foreigners and did not originate from among the negative black population.

The same paper reveals that sera from the population, collected over several years and observed in good conditions, had been negative against AIDS antibodies up to 1980, without exceptions. Only in 1980 the first positive sera were noted. It should be recalled, that literature reports on the first clinical AIDS cases in Central Africa in December 1982. With an incubation period of 2 years the first infections must have taken place towards the end of 1980, which excludes the origin of AIDS in Africa.

Biggar[72], an authority in the field of epidemiology, also regards AIDS as a new disease in Africa, with the first clinical cases in 1983, or maybe in 1982, with the presumable date of infection around 1980. Accordingly the disease appeared in Africa around the same time as in Europe, and there is no evidence of an African origin of AIDS. "In my talks with clinical specialists who had worked in tropical Africa during the Sixties and Seventies they always expressly stated that AIDS would undoubtedly have been clinical ascertained, if it had appeared otherwise than in sporadic exceptional cases."

The specific climatic situation of Central Africa

Concerning the time of the appearance of AIDS, the frequency of the disease and the contamination of the healthy population, Central Africa may therefore be compared with the states of Western Europe. This is astonishing in so far, as there are practically no risk groups mainly contributing to the prevalence of AIDS in Central Africa. Homosexual men, who contribute most to the prevalence of AIDS by their promiscuity - in many cases with several sex partners per night - and with the particularly great danger of infection in anal coitus, are almost non-existent in Central Africa. Drug addicts passing on AIDS with non-sterile needles may practically be excluded, because hard drugs are financially out of reach for the largest part of the population. The main channel of entry for the virus was presumably stored blood from the USA. This was distributed to an equal extent among men and women, so that in Central Africa AIDS from the start appeared among both sexes in approximately the same proportions, whereas that equilibrium is only gradually beginning to be established in Western Europe.

Female prostitution and the men making use of it represents the main risk group in Central Africa for AIDS as well as for venereal disease. That risk condition is above all concentrated in urban centres.

If Central Africa still keeps pace with Western Europe in the development of AIDS, despite the absence of risk groups, other specific risk factors must be present. These become manifest in the light of a climatic investigation of the problem.

Most of the states mentioned in connection with AIDS in Africa - Zaire, Gaboon, Ghana - are entirely, or in part, situated in the tropical rain forest zone which runs across the largest part of the African continent. In the north this borders on the arid Sahel zone, from which so far no AIDS cases have been reported. In the south of Africa there is an extensive prairie region in which AIDS cases have also not occurred up to now, with the exception of white homosexuals

will be of interest.

Table 2

Prevalence of LAV/HTLV-III positive serum in different parts of South Africa (Sher[73])

Serum samples from	Numer of samples	Positive samples	
South Africa, white nursing staff	150	0	0 %
black blood donors	1740	5	0.3 %
Botswana	35	1	3 %
Swaziland	22	0	0 %
Lesotho	164	0	0 %
Transkai	240	4	1.6 %
Zimbabwe	500	4	0.8 %
Malawi	87	21	24 %
Zambia	661	119	18 %

The slight prevalence of the virus in large parts of southern Africa and the marked rise for Malawi and Zambia are conspicuous. Both those countries are north of the prairie zone to which the others belong. They do not have zones of tropical rain forest, but extensive marshland in the valleys of the Zambezi, the Kafue and Luangwa rivers and on the west bank of the Malawi lake.

We found a first indication of the relationship between immunodepression and tropical marshlands in the work of Whittle et al. They established that malaria tropicana (pathogene Plasmodium falciparum) reduced the control of the B-cells by the T4-cells. The number of T4-cells decreases, which results in a reduced immune activity. (Epstein[2], Bigger et al.[3], Gigase et al.[74], Taelman et al.[75] and Volksky et al.[76]).

The group associated with Gallo also reported on an immunosuppressive effect of malaria.

The larva of the Anopheles malaria mosquito exclusively breeds in stagnant water and is therefore dependent on bogs and pools. The relationship between immunosuppression and tropical swamps is therefore evident [illegible]

similar relationship between the endemic spreading of the Kaposi's sarcoma and the swamps of southern Europe.

Malaria, however, is not the only immunosuppressive factor in tropical Africa. McFarlane[77] mentions, apart from malaria, leishmaniosis, filariosis, schistosomiasis and different helminthic and amoeba infections. In addition there are bacterial diseases such as tuberculosis and leprosy, and numerous virus infections by hepatitis B-virus, Epstein-Barr virus, cytomegalovirus, etc.

Living conditions can also weaken the immune defence. In Africa the nourishment, poor in proteins, could play an important part. McFarlane underlines that the thymus is the first organ damaged by undernourishment, and this gland is the source of the formation of T4-cells.

All obstructions of the immune defence may favour the outbreak of a full-blown AIDS. We must not forget that the clinical course of AIDS corresponds to a race. After an infection by LAV/HTLV-III the affected T4-cells proliferate and cause lymphadenopathy, which will spontaneously heal in 90 per cent of all cases, because the reproduction of the virus is checked by the formation of antibodies. Only in about 10 per cent of all cases the immune defence are inadequate. In those cases it will be paralysed, because the virus will destroy the T4-cells, giving green light to the Kaposi's sarcoma and the opportunistic infections. Every additional immunosuppression from other sources, malaria, schistosomiasis, etc., will therefore increase the proportion of the lymphadenopathies transforming into full-blown AIDS.

In order to obtain a full understanding of the complex of co-operative reciprocal effects which favour the spreading of AIDS in Africa, we need to deal with the circumstances, that viruses generally do not attack cells in a state of rest. LAV/HTLV-III as well is evidently inactive in regard to dormant T4-cells, since the virus cannot be cultivated on them. For virus cultivation the cells need first to be "activated", i.e. they must be placed in a condition of permanent irritation which will allow the viruses to penetrate into the cells and to

A completely healthy organism therefore is not likely to be infected by AIDS. If its T4-cells however have to combat any pathogene, becoming activated in the process, the T4-cells will become receptive also to the AIDS virus. Probably any pathogene to which our organism reacts by the formation of antibodies can activate the T4-cells, thereby paving the way to AIDS. In Central Africa, however, there is a generally higher gammaglobulin level than in Europe, which shows that the African population has to deal more frequently with infectious diseases than Europeans, and that their T4-cells are more often in a state of activity than ours (McFerlane[77]).

Lack of protein, diseases with an immunosuppressive effect and the frequency of trivial infections in the tropical forest belt of Africa may be considered as an additional factor favouring the spreading of AIDS. This explains, how this syndrom can spread in Central Africa at a similar rate as in Europe, despite the absence of homosexuality and drug addiction.

. . .

Concluding remarks

The epidemiological specific features of AIDS in Africa can today be completely explained. Nothing speaks in favour of the development of AIDS in Africa by natural ways. On the other hand there are indisputable substantiating facts to show that AIDS appeared in Africa at about the same time as in Europe, with some delay as compared to the USA.

The structure of the LAV/HTLV-III genome and of that of other retroviruses is today adequately known, so that we can exclude the possibility that the AIDS virus had naturally evolved from a HTLV virus - of man or monkeys. Nor could the AIDS virus have naturally evolved from the Visna virus by way of a series of mutations. The AIDS virus contains a proportion of HTLV and a proportion of lentivirus, which, according to our present standards of knowledge, could only have been combined by means of gene surgery. This is also indicated by

The first appearance of AIDS exactly coincides with the opening of a P-4-laboratory at Fort Detrick - taking into account the incubation period. This is also indicated by the fact, that the spreading of AIDS to the world emanated from New York, a city in the neighbourhood of Fort Detrick. The assumtion that AIDS is a product of the preparation of biological warfare can therfore be quite plainly be expressed.

Fig. 1: The genomes of the LAV virus (above) and of HTLV-I (below) according to Wayne-Hobson, Alizon and Montagnier (4).
The inscription of the square below, right, should, according to latest standards, read: tat/pX

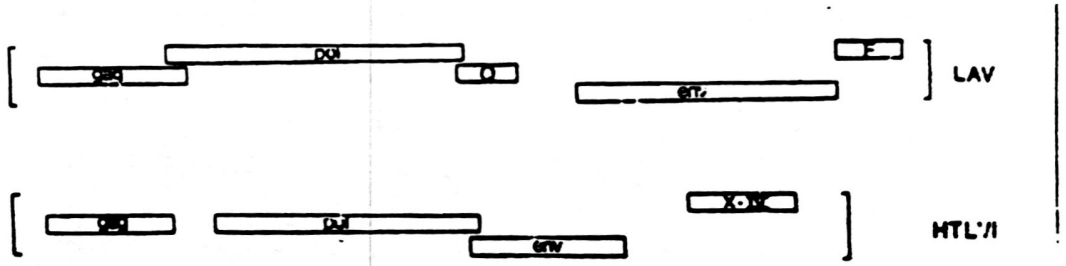


Fig. 2: Heteroduplex-hybridisation of the HTLV-I, LAV/HTLV-III and Visna virus genomes. Above: the electronmicroscopic picture, below: the graphic interpretation (Gonda et al.[20]).

A and a: heteroduplex of HTLV-I and LAV/HTLV-III

B and b: heteroduplex of HTLV-I and Visna virus

C and c: heteroduplex of LAV/HTLV-III and Visna virus

D and d: heteroduplex of LAV/HTLV-III and Visna virus, with LAV/HTLV-III component implented in reversed position

In A and B arrows mark the hybridised sections

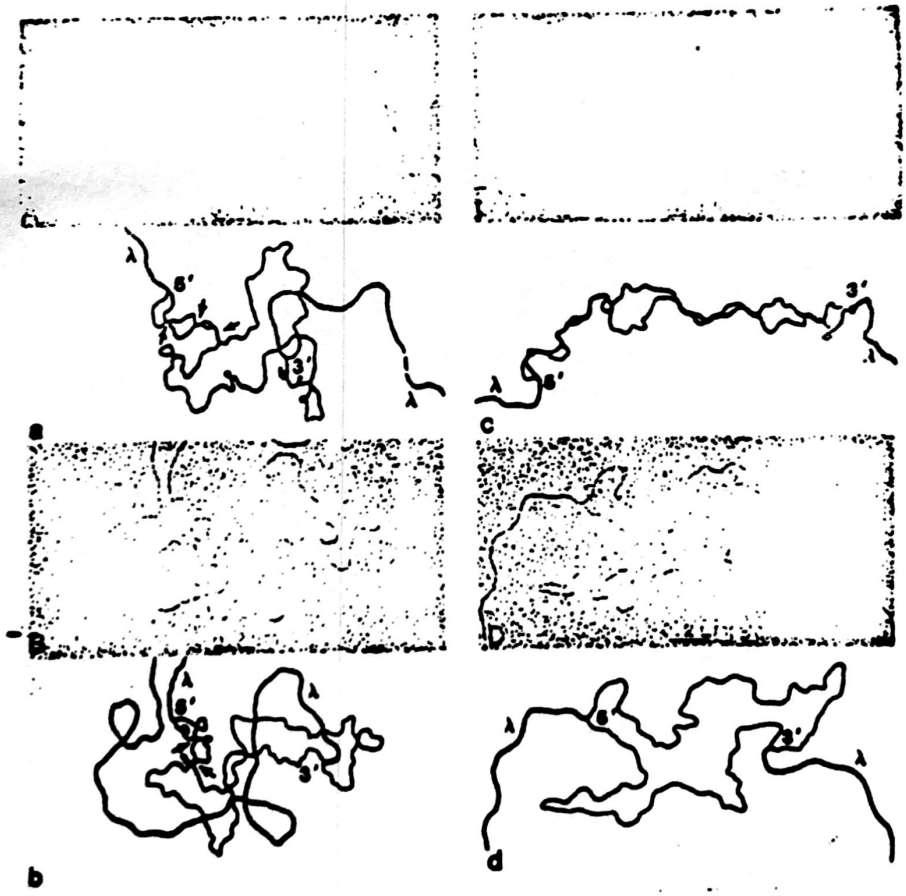


Fig. 3: Comparison of the 3'end of the genome of HTLV-I and a virus of the rhesus monkey. Not the nucleotides are marked, but the aminoacids coded by nucleotide tripletts.
The ranges identical in both genomes are framed (Watanabe et al.[25]).

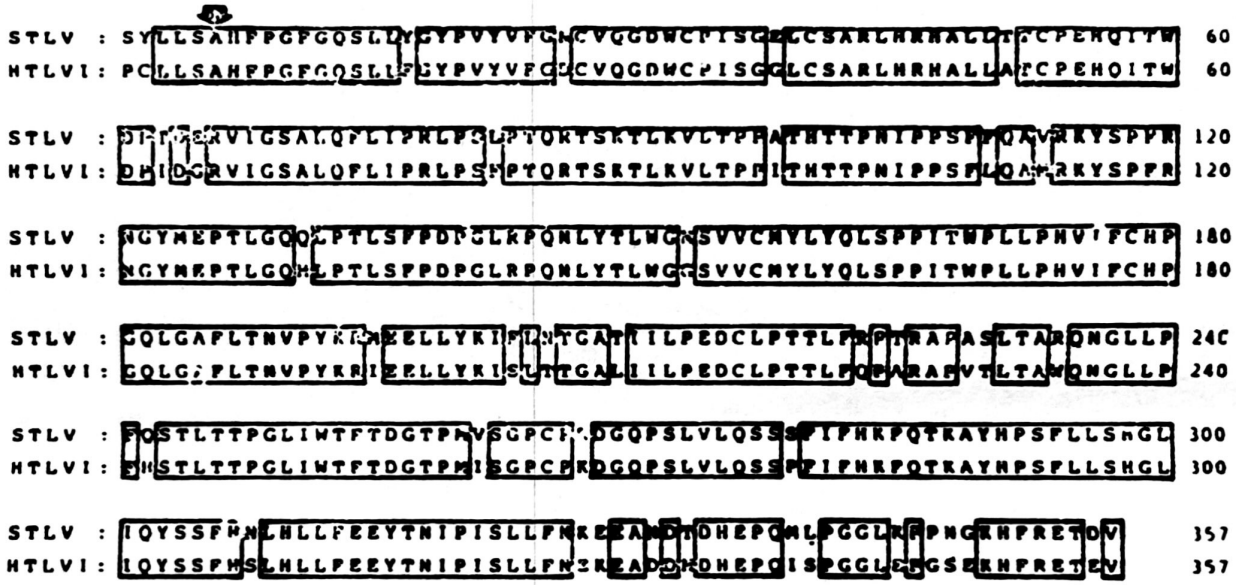


Fig. 4 : Presumable phylogenetic tree of the HTLV-family, deduced from the homologies of the virus genomes. (Watanabe et al.[25]).
The AIDS virus HTLV-III presumably branches off much sooner from the common ancestor virus

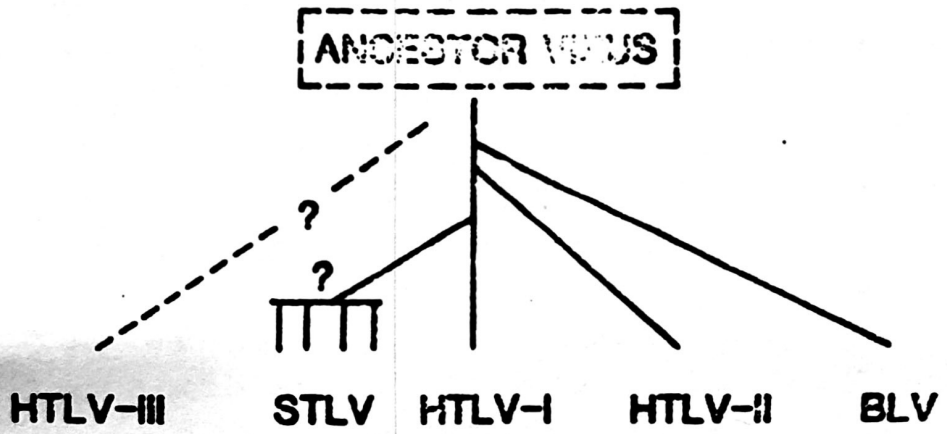


Fig. 5: Conditions for the immune reactions in fresh and partially denatured sera. The curves denote the specificity range of the antibodies. The squares indicate the reaction of the ELISA and Western blot test.

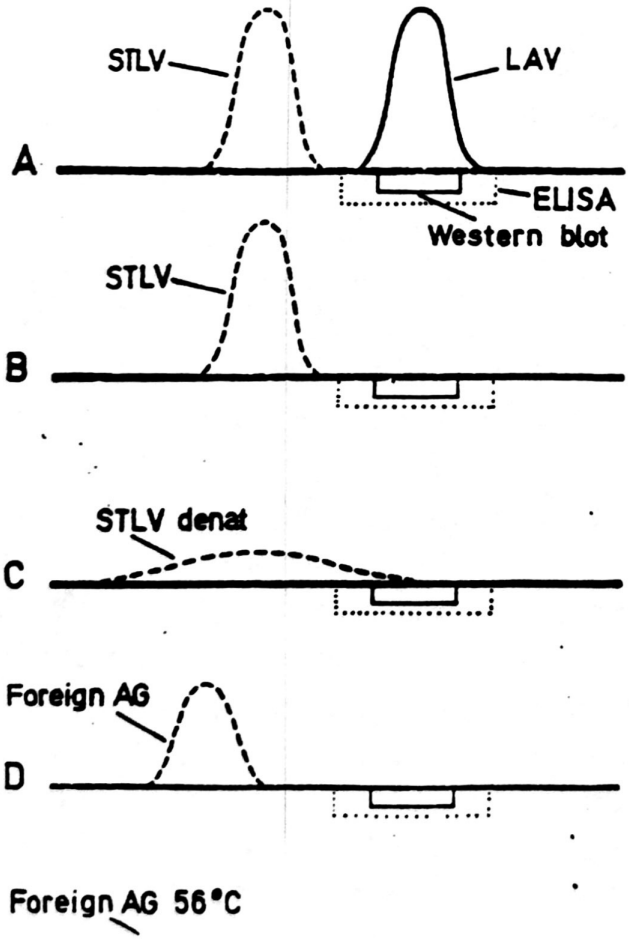
A: fresh serum with antibodies against LAV and against the STLV monkey virus
LAV yields a powerful reaction to ELISA and Western blot

B: fresh serum without LAV, but with STLV-antibodies:
no reaction to ELISA and Western blot

C: serum with STLV-antibodies, partly denatured due to inadequat conservation:
weak reaction to ELISA and Western blot

D: serum without antibodies against LAV, but with antibodies against alien antigenes, unheated:
no reaction to ELISA and Western blot

E: the same serum, heated to 56°C for 30 minutes:
weak reaction to ELISA, no reaction to Western blot



Our study on the origin of AIDS includes the scientific papers related to AIDS up to April 1986. Since then, the International Conference on AIDS, held in Paris in June 1986, has brought forward much new information, with which we feel bound to confront our thesis concerning the American origin of AIDS. Jane P. Mitchell et al. (Poster 263, p. 23) are the only ones who try to provide evidence in favor of an African origin of AIDS. They report the isolation of an LAV/HTLV-III- like virus from a serum collected in Central Africa in 1976. But they find important differences in the range of proteins: 31K to 55K, 55K to 80K and 120K, as well as in the restriction pattern and in the Western Blot reactions as compared with sera from LAS patients from the USA.

A. Sonnerborg et al.(Poster 15, p 17) probably deal with the same isolate. They state: "the restriction cleavage pattern of the virus is clearly distinct from other viral isolates including more recent isolates from Zaire."

Thus, we cannot consider the isolation of such a virus as evidence for the prevalence of AIDS in Zaire as early as 1976. On the contrary, numerous modern studies point to recent appearence of AIDS in Africa. We cannot analyse every one of the different authors. We begin with the statement of:

J.M.Mann.(Communication 49,p.109)

1) "LAV/HTLV-III is a relatively new pathogen in these urban settings."
2) " Early reports....contained inacurate estimates of antibody prevalence because of a large proportion of false-positive ELISA tests."
3) " There is no evidence, that LAV/HTLV -III in Africa is more virulent than the same virus in the USA/ Europe."
4) " The rate of seroconversion to LAV/HTLV-III among heterosexuals in Africa is considerably lower than among male homosexual populations in USA/Europe."

When we wrote our study on AIDS, data related to the prevalence of LAV-infections in different African states were very scarce, and often based on estimations. Now we have reliable data at our disposal:

P.Piot et al. (Communication 50, p.lol)

1)" Our results indicate that AIDS-virus was introduced recently into Kenya... by contiguous spread from the West."

2) The high seroprevalence rates in the general population of Kenya, as reported by others, were not confirmed."

K.Riba, J.M. [illegible] et al.(Communication 51, p. lol)

"Overall rates of annual progression from asymptomatic LAV/HTLV-III seropositivity.... closely approximate estimates from studies in the United States and Europe."

S.H. [illegible] et al.(Communication 52, p.lol)

"Opportunistic infections with immunodeficiency caused by HTLV/III/LAV retroviruses have appeared in Africans in significant numbers only within the past 3 years"

Prevalences of antibodies against LAV/ HTLV-III between 0 and 1% have been reported by:

E. Beth-Grivalle et al.(Poster 367, p.128)
for Tunesia.

A. Froment et al.(Poster 368, p.128)
for a remote area of Cameroon

M. Merlin et al.(Poster 374, p.129)
for 6 African states, with an especially low prevalence in the Sahelian area.

E.Delaporte et al.(Poster 375, p. 129)
for the rural population of Gabon.

J.P.Duran et al.(Poster 377, p. 13o)
for 3 regions of Cameroon.

J.E.Walkin et al.(Poster 379, p. 13o)
for an unnamed urban area in the Subsahelian zone.

F. Titti et al.(Poster 38o, p. 13o)
for Mogadishu, Somalia.

These estimates ought to be further reduced by taking into account the effect of blood transfusion, medical injections or scarifications, often required by the high prevalence of sickle cell anemia and numerous infectious diseases.

A. Weiss et al. (Poster 374, p.129)
B. Delaporte et al. (Poster 379, p.130)
H. Kuhlmann et al. (Poster 381, p. 129)

J. Desgranges, Montagnier et al. (Communication lic, .p.1c6) once more dealt with the African sera. 8c5 sera collected in 197c showed a prevalence of 2,1% with ELAVIA- Pasteur, but 36% with Abbott-ELISA. The 17 (2,1%) positive sera were reexamined by immunofluorescence, RIPA and competitive ELISA (Wellcome). Only 2 of these sera (0,oo2%) gave positive results, and a virus isolation failed in both of them. There were obviously no LAV/HTLV-III viruses in the 197c batch of sera.

In our study we suggested, that the false-positive ELISA results in old sera might be due to cross-reactions with the Green-Monkey virus prevalent in many humans.

Ch. Rouquoux, F. Brun-Vézinet et al.(Poster 375,p.13o) studied 34c sera from 1975-1978, collected from a Pigmy population. Only 2 of them appeared positive in Pasteur-ELAVIA none of them was positive in Western Blot and RIPA. The authors emphasize the fact, that, though several species of Cercophitecus live in the Itturi-Forest and are hunted and eaten by the Pigmie, there is no C. aethiops, the African Green Monkey, which avoids the dense forests. Thus, there is no opportunity for cross reactions with the Green Monkey Virus.

S. Maayan et al.(Poster 3c6, p. 133) studies the sera from 244 Ethopian immigrants to Israel. 4o, (16,4%) of them appear AIDS-positive in an EIA-test, while while they are all negative in the Western Blot. Thus, they do not carry the AIDS-virus, but many of them carry an apathogenic virus crossreacting with LAV in a poorly selecting test system. In this case, they might be reacting with the Green Monkey Virus.

In order to compare the prevalence of AIDS in Africa and in USA, we opposed the differentestimates for Kinshasa, often called "the African AIDS inferno", at most some 3o patients in 1oo.ooo inhabitants, with data for San Francisco, which we estimated to be near to 3oo patients in 1oo.ooo inhabitants.

C.F. Rutherford et al(Poster 68o, p. 152)
write that on December 31st 1985, there were 1631 declared patients, corresponding to 2-o : 1oo,ooo, slightly less than our estimation. In the town of Belle Glade (Florida).
L.Montagnier, Gheysen et al.(Poster 33% p.86)
conclude an extensive study with the words: "No major differences in anti-HTLV-III/LAV antibody were observed between patients belonging to the known risk groups (in the USA) and patients originating from Africa".

This ought to put an end to the story of the African Origin of AIDS, and
T.M.S. Lee and E.A. Friedman(Poster 524, p.61)
conclude quite correctly: "New York City is the epicentrum of the world AIDS pandemic."

Nobody at the Paris Conference repeated the legend of the African Green Monkey Virus as a possible progenitor of AIDS.
Vanessa Hirsch, Hunsy and Rosen et al.(Poster 2o,p.18) and
H.R. Goldenblook, Gallo et al. (Poster 9, p. 16)
only indirectly support this hypothesis without mentioning it, by demonstrating common epitopes between the simian and the human virus in: p18, p24, gp41 and gp12o. But these proteins correspond to the gene groups: gag,pol and env, all related to the 5' half of the genome which, in the chimera of HTLV-I and visna belongs to the HTLV-part. No cross reaction with the genes of the 3' end, belonging to the visna part of the genome, were reported by the authors.

Other authors categorically oppose the green monkey story.
J.Schneider et al.(Coomunication 73, p.1o)
thoroughly studied the different cross reactions of HTLV-III with STLV-III-agm and the ~~monkey~~ STLV-IIImac. They conclude : "... the human and the monkey virus are quite distinct and therefore the one cannot be a recent progenitor of the other."
R.C.Desrozier, Letwin et al. (Communication 74,p.1o)
even find besides differences in the genome structure, slightly different ultrastructural feature.They conclude that the human and the monkey retroviruses are not genetically or immunologically closely related.

Under these conditions, the assertion of Essex and his team, that there is hardly any difference between HTLV-III and STLV-III-agm cannot be agreed with.
[illegible] and N.L. Letvin. (Communication 76, p.10)
[illegible]. (Communication 133, p.14)
study the immunological and pathogenetical behaviour of these two viruses. Thus, STLV-III does not grow in human B-lymphocytes transformed by EBV. On the other hand, the neutralizing antibodies, which are bound to stable epitopes of gp120 and thus inhibit the fixation of the virion on the target cell, are different in both viruses. The neutralizing antibody from an AIDS-patient inhibits the infection *in vitro* by LAV/HTLV-III, but not by STLV-III, while antibodies against HTLV-I or STLV-III have no neutralizing effect upon LAV/HTLV-III.

These experimental data confirm our previous point of view, namely that, from every consideration, the transformation of the green monkey virus into the human AIDS virus remains biological nonsense.

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